REMARKS

Claims 1-54 are currently pending. Claims 9, 19, 29 and 48 are amended. Support for the amendment is found at least in Col. 4, lines 36-61.

The Examiner notes that the Preliminary Amendment does not comply with 37 C.F.R. 1.173(b) as the added claims were not underlined. Applicants submit herewith an underlined version of claims 9-54 in compliance with 37 C.F.R. 1.173(b) as noted by the Examiner. As required by 37 C.F.R. §1.121(c), the amended claims are rewritten with all changes included. In addition, as permitted under 37 C.F.R. §1.121(c)(3), a clean version of all the pending claims is submitted as a single amendment paper, which is attached to this response. Also attached is the marked-up copy of the claims, marked to show all of the changes relative to the previous version of the claims.

Applicants gratefully acknowledge that claims 6-8 are allowed.

Offer To Surrender under 37 C.F.R. § 1.178

The Examiner states that the reissue application was filed without the required offer to surrender the original patent. However, Applicants respectfully state that the Offer to Surrender Declaration was executed on September 7, 2001 and mailed to the Examiner on December 31, 2001 in Response to Notice to File Missing Parts for Reissue Application. A copy of the Offer to Surrender Declaration is attached hereto.

Double Patenting Rejection

Claims 11, 21, 31 and 48-54 are rejected under Section 101 as claiming the same invention as that of claims 1 and 2 of US 5,814,632. Applicants respectfully traverse this rejection.

Claim 1 of US 5,814,632 is directed to a method of treating diseases, including sepsis, with a composition consisting of riboflavin and/or a riboflavin derivative.

Claim 2 of US 5,814,632 is dependent on claim 1 and recites that the composition is administered in an amount of 0.5-500 mg/kg.

Claims 9, 19, 29 and 48 of the instant reissue application are amended to indicate that the composition comprising riboflavin and/or riboflavin derivative includes a composition formulation additive.

With this amendment, Applicants respectfully submit that this rejection is now moot.

Rejection of Claims 1-5, 9-14, 18-24, 28-34, 38-43 and 47-54 Under 35 U.S.C. § 103(a)

The Examiner is of the opinion that the above listed claims are unpatentable over Salatijants (B) and Bounous *et al.,* (A) in view of Windholz *et al.,* (R) (The Merck Index)

This rejection is respectfully traversed. A brief discussion of the present invention will be of assistance in appreciating the Applicants' reasons for traversal of the rejection.

Riboflavin (vitamin B_2) has been conventionally employed as a growth-accelerating factor. With respect to riboflavin deficiency, the following disclosure appears on column 1, lines 53-58 of the present patent specification:

In the case of humans, it is known that the lack of riboflavin leads to cheilitis, acute chronic eczema, solar eczema, seborrheic eczema, conjunctivitis, angular cheilitis, glossitis, pellagra or the like. Accordingly, riboflavin is used for preventing and treating these deficiency diseases of vitamin B_2.

The present invention (Claims 9, 19, 29, 39, 48, and 52 and claims dependent thereon) is based on the discovery that riboflavin (vitamin B2) and/or riboflavin derivatives have an effect on the immune function. (Refer to column 2, lines 11-21 of the present patent specification.)

Reference B (Salatijants, U.S. Patent No. 4,708, 952 (the "'952 patent")) relates to a composition adapted to *prolong the residence time of drugs in circulating plasma* of mammals including humans comprising (Column 1, lines 56-64):

Hexanoic Acid

Potassium Hydrogen Tartrate

Tannic Acid

Pectin

Riboflavin

and either

glutamic acid

or

L-tyrosine

In fact, what is claimed in the '952 patent is a composition containing six components adapted to prolong the residence time of drugs in the circulating plasma of mammals. The composition with the six components only prolongs the residence time of the drug, the active ingredient. In contrast to the opinion of the Examiner, nowhere does the '952 patent teach the immunopotentiating effects of riboflavin or derivatives thereof. Therefore, the reference (B) composition is thus irrelevant to "enhancing the immune function." Not only does the '952 patent not teach riboflavin for "enhancing the immune function" as recited in claims 19, 29, 48, and 52 and claims dependent thereon, the '952 patent also does not even recognize this function. Moreover, the '952 composition comprises at least 5 indispensable ingredients other than riboflavin including also the active drug used in the actual treatment the disease of the mammal. It is therefore not obvious to one skilled in the art that riboflavin alone and not one of the other five ingredients is essential in treating the disease. Therefore the present invention as recited in claims 9 and 39 and the claims dependent thereon is neither disclosed nor suggested by the '952 patent.

Reference A (Bounous *et al.,* U.S. Patent No. 5,290,571 (the "'571 patent")) is directed to a whey protein composition. Bounous *et al.,* state (column 5, lines 34-56):

> A suitable source of whey protein concentrate is the material known by the trademark PROMOD. It has the following nutrients:

Protein

Fat

Carbohydrate

Water

Calcium

Sodium

Potassium

Phosphorus

Additionally, Bounous *et al.*, laboriously list all components (column 5, line 42 to column 6, line 31):

> It [Whey protein] has the following typical amino acid composition per 100 g protein:
> Essential Amino Acids:
> Histidine, 1.9 g; Isoleucine, 6.2 g; Leucine, 10.8 g; Lysine, 9.3 g; Methionine, 2.2 g; Phenylalanine, 3.6 g; Threonine, 7.3 g; Tryptophan, 1.9 g; Valine, 6.0 g.
> Non-Essential Amino Acids:
> Alanine, 5.3 g; Arginine, 2.6 g; Aspartic Acid, 11.2 g; Cysteine, 2.6 g; Glutamic Acid, 18.2 g; Glycine, 2.1 g; Proline, 6.5 g; Serine, 5.6 g; Tyrosine, 3.4 g

While it is true that Bounous *et al.*, asserts to teach "a method for improving the humoral immune response in mammals" (see column 11, lines 32-33) they go on to clearly teach that the "biological activity is based on the overall amino acid and associated small peptides pattern resulting from the contribution of all its protein components." (See column 11, lines 37-40). Further, they state, "[r]ecent observations have revealed to us that the described biological activity of the whey protein concentrate, already shown to be unrelated to its nutritional quality, is actually dependent on the undenatured conformation of the proteins." (See column 16, lines

63-67). Thus, Bounous *et al.,* clearly teach that the humoral immune response is attributable to the undenatured condition of the proteins.

Additionally, Bounous *et al.*, state:

> Individually the effect of each of the vitamins (vitamins B1, B2) in whey protein fed mice is limited; however, their synergistic effect on the immune response of whey protein fed mice is apparent (FIG. 11, diets 5, 6 and diet 1). The same *vitamins* are *ineffective* on the immune response of casein diet-fed mice. (Emphasis added)

With this statement, Bounous *et al.,* attribute the immune response to the protein and *not* to the vitamin B_2 and therefore teach away that vitamin B_2 *alone* enhances the immune response. For this reason, the present invention is neither disclosed nor suggested by Bounous *et al.*

The Examiner further cites Windholz *et al.*, The Merck Index, (1983), abstracts nos.: 600, 8099 and 8100, Reference R, (the "Merck Index") in support of the alleged rejection under 35 U.S.C. § 103(a). Treatment of infections with antibiotics has many well known deficiencies. Regarding such deficiencies, please see column 1, line 64-column 2, line 3 of the present patent specification, for example. Thus when an antibiotic is used continuously, resistant bacteria are generated and the efficacy of the antibiotic is lowered, however, the massive administration of antibiotic as a countermeasure is accompanied by problems of retention of the antibiotic and a further increase of resistant bacteria.

One solution to overcome the above-described problems caused by antibiotics is solved by the present discovery of the composition comprising riboflavin and/or riboflavin derivatives. The Applicants state:

> In view of the above-described problems involved in antibiotics, the present inventors have carried out an extensive investigation for a long time with a view toward developing an infection protective agent safe for humans or animals. As a result, it has been found that riboflavin and/or

> riboflavin derivatives have an action to potentiate immune function, and also that water-soluble polymers and the like have an action to enhance and sustain the immune-function-potentiating action of riboflavin and/or the riboflavin derivatives, leading to completion of the present invention. (see column 2, lines 11-21 of the present patent specification).

As disclosed in column 2, lines 35-43 of the present patent specification, synergism is achieved by the combined use of riboflavin and/or the combination of a riboflavin derivative and antibiotic. This fact (significant synergism) is substantiated by example 4 and Table 5, wherein amoxicillin (AMPC) is used as the antibiotic.

Reference R (The Merck Index 10th Ed. pp. 83-84 Abstract No. 600 (1983)) merely discloses the antibacterial properties of amoxicillin. Reference R, however, neither discloses nor suggests the combined use of riboflavin and/or a riboflavin derivative and an antibiotic. Needless to say, Reference R does not at all disclose or suggest any synergism by such combined use. Reference R is thus irrelevant to the present claims.

The examiner also rejects claims 4, 13, 23, 33, 42, 50 and 53 by indicating that the "determination of a dosage having optimum therapeutic index is well within the level of one having ordinary skill in the art." Applicants respectfully traverse this rejection. The cited references do not teach the method claimed as applicants' invention. Applicants respectfully submit that they are entitled to claim various dose ranges in this patentable method of treatment claims.

In view of the foregoing, Applicants feel the rejections are now moot and should be withdrawn.

CONCLUSION

Applicant respectfully requests reconsideration of the application in light of the remarks made herein. If the examiner believes that a telephonic interview would expedite the allowance of the application, the Examiner is invited to contact the undersigned attorney at the number below.

Respectfully submitted,

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Date: March 4, 2003

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